ABSTRACT

WNT10A plays a role in the proper proliferation and differentiation of ectodermal structures. Mutations in this gene can be responsible for a highly phenotypically variable range of disorders termed *ectodermal dysplasias*. Here, we describe the case of a five-year-old male patient who is mosaic for Turner syndrome (45,X [90%]/46,X isodicentric Y [10%]) and who presented to dermatology with anhidrosis, conical-shaped teeth, and a slowed rate of hair growth with genetic testing subsequently revealing a likely pathogenic heterozygous variant in *WNT10A* (c.682T>A; p.Phe228Ile). Future investigation into the *WNT10A* pathway, which is regulated downstream by β-catenin, might allow topical therapeutics to be developed that promote normal ectodermal growth and differentiation. Current management for this patient includes precautions taken to prevent overheating and heat stroke and close dermatological and dental monitoring.

KEY WORDS: Ectodermal dysplasia, Turner syndrome, sweating, WNT proteins

WNT10A Mutation Causes Ectodermal Dysplasia in a Patient Mosaic for Turner Syndrome

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J Clin Aesthet Dermatol. 2020;13(6):57–58

WNT proteins belong to a highly conserved family of signaling molecules involved in processes during embryogenesis and homeostasis in adult tissues.[1] Ectodermal structures, including hair follicles, nails, teeth, and sweat ducts, use *WNT10A* specifically as a critical ligand controlling proliferation.[1] Therefore, *WNT10A* mutations can present with an overlapping spectrum of ectodermal signs and symptoms, including aberrant hair texture, nail dystrophy, tooth agenesis and misshaped teeth, and hypohidrosis.[2] This *WNT10A* ectodermal dysplasia manifests variably between the sexes and depends on patient age.[3,4] For example, certain features of *WNT10A* mutations, such as tooth anomalies, seem to be more prevalent in heterozygous males, whereas hair and nail pathologies are more common in female heterozygotes.[5,6] Incomplete penetrance can also occur. Here, we describe the unique case of a five-year-old male patient who is mosaic for Turner syndrome and who presented with anhidrosis, conical-shaped teeth, and a slowed rate of hair growth, in the absence of other severe ectodermal abnormalities, due to a *WNT10A* gene mutation.

CASE PRESENTATION

A five-year-old male patient presented to dermatology for an evaluation of anhidrosis, which had been present since birth. He reported becoming quickly overheated and flushed when outside in the summer, requiring him to have consistent use of air conditioning and fans to stay comfortable. A subsequent review of systems for other signs and symptoms associated with ectodermal dysplasia was performed. The patient was positive for conical-shaped primary teeth (Figure 1) and slower-growing hair compared to other family members. No abnormalities were identified in the eyebrows, eyelashes, or nails. Further dental evaluation revealed the presence of normal adult permanent teeth on X-ray, without other abnormalities.

The patient's past medical history was significant for a chromosomal abnormality (45, X [90%]/46, X isodicentric Y[10%] mosaicism) which had caused developmental, genitourinary, gastrointestinal, cardiac, endocrine, and ear, nose, and throat complications since birth. These complications included a speech articulation disorder, mild motor delays (walked independently at 19 months), ambiguous genitalia, recurrent urinary tract infections, eosinophilic esophagitis, recurrent vomiting, bicuspid aortic valve, mildly dilated ascending aorta and aortic root, growth failure, poor weight gain, and recurrent otitis media. The patient's family history was significant for peripheral neuropathy in his mother. There was no family history of ectodermal dysplasia and no other family members had ever reported problems with sweating or other ectodermal structures. The patient reported having a three-year-old sister and seven-year-old brother who showed no significant medical concerns.

Upon suspicion for possible hypohidrotic

FUNDING: No funding was provided for this study.
DISCLOSURES: The authors have no conflicts of interest relevant to the content of this article.
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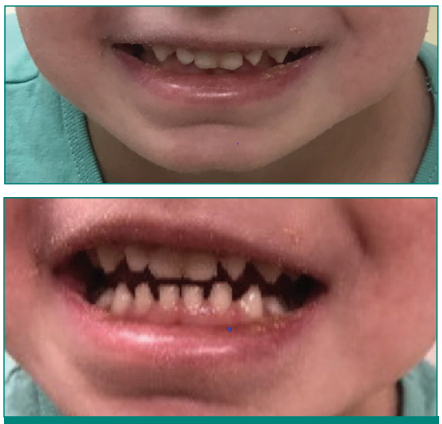

FIGURE 1. Conical teeth of a five-year-old patient. No dental abnormalities were found in the adult teeth on X-ray.

ectodermal dysplasia, genetic testing was performed. A likely pathogenic variant in *WNT10A* on chromosome 2q35 was identified in the patient—one that commonly presents with hypohidrosis, sparse scalp and body hair, and either missing or malformed teeth. Given that this mutation and resulting condition can be inherited in an autosomal dominant or recessive manner, the parents of the patient were advised to undergo family variant testing to determine if the finding in this patient was *de novo* or inherited. Family variant testing revealed the patient's father to have the same variant. However, his father was asymptomatic, stating he never had peg teeth nor sweating abnormalities, thus showing the reduced penetrance of the condition. Testing of his siblings was also offered if they were to develop symptoms or they wanted more information before future reproduction. After diagnosis, this patient was counseled appropriately on the necessary precautions that need to be taken for hypohidrotic individuals. These patients can more easily suffer from heat exhaustion or stroke, with a risk of death, if they do not remain adequately attentive to external environments and temperature. This patient was advised to avoid most outdoor activities, keep air conditioning in all classrooms, and ensure his home and sleeping environment are cool. He has also been counseled extensively on the importance of minimizing strenuous exercise and exposure to sun. Finally, a discussion of additional physical manifestations arising in adolescence, along with the social challenges of participating in sports and other activities, was had with the family. Conducting yearly dermatological visits to monitor the skin, hair, and nails was also advised.

DISCUSSION

The *WNT10A* gene spans 13.4kb on chromosome 2q35. It has four exons and encodes a messenger RNA of 2.4 kb.[6] The molecular pathway of this gene has been partially elucidated through the study of human and mouse mutant palmoplantar and tongue epithelia. In mouse and chicken embryos, *WNT10A* has been shown to be upregulated in skin and hair follicle morphogenesis as well as the oral epithelium in the first steps of tooth development.[7–9] *WNT10A* is a ligand that controls downstream β-catenin pathway activation.[1] β-catenin complexes with KLF4, a transcription factor required for epidermal differentiation. This complex then becomes a catalyst for epithelial proliferation and region-specific differentiation, allowing for the expression of specialized keratins required for normal tissue structure and integrity.[1] This pathway has led some to suggest that the topical application of appropriately formulated small-molecule WNT/β-catenin pathway activators could be a potential future therapeutic option for these patients.[10]

Patients with mutations in *WNT10A* have been reported to suffer from microdontia of the primary teeth, defective root and molar cusp formation, an absence of adult dentition, palmoplantar keratoderma, thinning hair, sweating abnormalities, a smooth tongue surface, and defective nail growth.[1] Specific *WNT10A* ectodermal dysplasia syndromes, such as odonto-onycho-dermal dysplasia (OODD) and Schöpf-Schulz-Passarge (SSP) syndrome, also exist.[11] OODD is characterized by severe oligodontia, nail dystrophy, hypotrichosis, erythematous lesions of the face, a smooth tongue with reduced fungiform and filiform papillae, and palmoplantar hyperkeratosis with increased sweating. SSP also has the manifestation of numerous cysts along the eyelid margins.[12] Our patient did not meet criteria to be diagnosed with OODD or SSP, but instead a unique variant resulting from abnormal *WNT10A*. Our patient was also a mosaic for Turner syndrome (45, X [90%]/46, X isodicentric Y [10%]). There does not seem to be any reported link between the two.

With regard to his ectodermal dysplasia, our patient had anhidrosis, misshapen primary teeth, and slower-growing hair. However, his other findings were relatively benign. Given that many of these manifestations can present in adolescence or later on, it remains less clear how his symptoms might appear in the future. However, the symptomatic management of this patient will be pursued, particularly through highly vigilant dental and dermatological care. Perhaps further understanding of the molecular mechanisms of the *WNT10A* pathway can lead to therapeutic interventions targeted at promoting proper differentiation of the sweat glands, nails, teeth, and hair. This will allow for more tailored treatment options for this patient in the future.

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